



Small fibre function in patients with meralgia paresthetica [☆]

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Abstract

Introduction: Patients with meralgia paresthetica (MP) usually experience not only paraesthesias and decreased tactile sensation, but also painful dysesthesias in the distribution of the lateral femoral cutaneous nerve (LFCN). We aimed at assessing whether there is any functional impairment of small fibres of the LFCN in patients with MP. **Methods:** We carried out a clinical, psychophysical and neurophysiological study in 14 patients with MP and 14 healthy control subjects. We assessed pain in the last 2 months, thermal thresholds and small fibres conduction by using a visual analogue scale (VAS-pain), quantitative sensory testing (QST) and contact heat-evoked potentials (CHEPs), respectively. Data were grouped for control subjects, non-affected side and affected side of patients with MP. **Results:** Patients marked a VAS-pain of 4.3 ± 1.5 . In the affected side, thresholds for warm and heat pain sensations were elevated and the amplitude of CHEPs was reduced in comparison to the non-affected side and controls (Bonferroni's test; $p < 0.001$ for all comparisons). The amplitude of CHEPs correlated inversely with duration of the symptoms ($r = -0.57$, $p = 0.002$), as well as with heat pain thresholds ($r = -0.18$, $p = 0.01$). No significant correlations were found between CHEPs and VAS-pain ($p > 0.05$ for all correlations). **Conclusion:** Besides the involvement of large myelinated fibres, partial loss of function in small fibres may also account for the painful symptoms of patients with MP, especially in those with longer disease duration.

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Keywords: Meralgia paresthetica; Small fibres; Contact heat-evoked potentials; Pain; Quantitative sensory testing

1. Introduction

Meralgia paresthetica (MP) is a mononeuropathy resulting from compression of the lateral femoral cutaneous nerve (LFCN) as it crosses the anterior superior iliac spine under the inguinal ligament to enter the thigh [21]. Affected patients usually experience deficit on tac-

tile sensation and painful dysesthesias over the cutaneous distribution of the nerve [22,42]. Abnormalities in nerve conduction studies [22] and somatosensory-evoked potentials [41] reflect large fibre dysfunction in the LFCN of patients with MP. However, neuropathic pain symptoms, such as dysesthesias, are associated with small fibre lesions [9,33,43].

Small fibre function can be non-invasively assessed by quantitative sensory testing (QST) for thermal sensation [48], in which warm and heat pain thresholds reflect the function of C- and A δ fibres, respectively. However this method is limited by the subjectiveness of the individual's responses. Contact heat-evoked potential (CHEP) is a

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more objective tool for the evaluation of small fibre function. The system delivers rapidly ramped heat stimuli, able to evoke cerebral potentials reliably [3,10,47] and has been used for the study of many pain syndromes [5,35,46,49].

The aim of our study was to analyze the function of small fibres within LFCN in MP patients compared to healthy control subjects by using psychophysical assessment of thermal thresholds (QST) and CHEPs.

2. Methods

The study was carried out in 14 patients with idiopathic MP aged 29–45 years (8 M and 6 F) and 14 healthy subjects aged 21–43 years (7 M and 7 F). The diagnosis of MP was based on clinical and electrophysiological criteria. The inclusion criteria were: (1) unilateral positive or negative sensory symptoms in the distribution of the LFCN and (2) sensory nerve action potential (SNAP) amplitude in the LFCN of the affected side reduced to less than 50% in comparison to the contralateral one. Patients were excluded when they presented with bilateral symptoms, had any clinical or electrophysiological sign of impairment in nerves other than the LFCN, or were being medicated with drugs that could potentially affect the nervous system.

Patients and controls underwent a conventional nerve conduction study (NCS), performed according to standard methods [20]. In patients, needle electromyography was done in at least one muscle per myotome from L3 to S1. Subjects gave their written informed consent for the study, which was approved by the Local Ethics Committee of Hospital Clinic of Barcelona and accorded with the Helsinki Declaration.

2.1. Nerve conduction study of the LFCN

The LFCN was stimulated in the medial part of the iliac spine, lateral to the femoral artery. The antidromic SNAP was recorded using surface electrodes 2 cm apart oriented longitudinally over the zone of LFCN at the anterolateral aspect of the thigh, at the middle part of an imaginary line connecting the anterior superior iliac spine with the lateral border of the patella. The stimuli were 0.2 ms duration delivered at 2 Hz from a constant-voltage source. Between 30 and 40 responses were averaged using a sampling rate of 2.5 kHz.

2.2. Quantitative sensory testing

Thermoalgesic stimuli were applied at the skin of the lateral aspect of both thighs (approximately 10–15 cm above the knee joint) with a Peltier contact thermode of 12.5 cm² (Somedic, Sweden) at a ramp rate of 1 °C/s. We used the method of limits [13] to determine warm and heat pain thresholds in all patients and cold thresholds in 8 patients. Thresholds were defined as the mean value of five stimuli separated by inter-stimuli intervals of at least 60 s [39].

2.3. Contact heat-evoked potentials

The contact heat-evoked potential stimulator (CHEP, Medoc Ltd., Ramat Yishai, Israel) has a Peltier thermode with a surface area of 572.5 mm². We used a target heat pulse

temperature of 41 °C to study C-fibre and 51 °C to study A δ -fibre [15,46], using a heating rate of 70 °C/s. For each investigation, 20 consecutive pulses were applied with random time intervals of 10–20 s. Contact heat-evoked potentials (CHEPs) were recorded from Cz with reference to earlobe (contralateral to stimulus), using silver/silver chloride cup electrodes of 9 mm diameter filled with a conductive adhesive gel. Signals were recorded using a Mystro5Plus electromyograph (Oxford Instruments, UK). For artifact control, we monitored the electrooculogram by supra- and infra-orbital electrodes.

2.4. Experimental procedure

We first did an interview approaching demographical (age, sex, weight and height) and clinical data, such as duration of disease, verbal pain descriptors and determination of a visual analogue scale for intensity of sensory painful symptoms (VAS-pain; 0 = no pain and 100 = maximal pain imaginable) in the last 2 months. Then, we carried out a standardized physical examination of motor and sensory functions, including clinical tests for dynamic and static allodynia. Finally, the psychophysical and neurophysiological tests were carried out by an independent examiner (P.S.), unaware of the results of clinical evaluation.

2.5. Data reduction and statistical analysis

In patients, data were grouped separately for the affected and the non-affected sides. In control subjects, because differences between sides were not expected for thermal thresholds [50] or CHEPs [45], data from both sides were pooled together. For NCSs of LFCN, latency, amplitude and conduction velocity were measured. Absent potentials were considered when SNAP amplitude could not be recognized after two averages of 40 stimuli. In this case, SNAP latency was not considered for analysis and SNAP amplitude was entered as 0. For QST, we calculated the grand mean and the standard deviation of threshold values for each group. For the CHEPs, two series of 20 artifact-free trials were selected and averaged offline. We measured the mean latency of N2 and P2 peaks, and their mean amplitude (N2/P2 amplitude).

We used one-factor repeated measures ANOVA for group comparisons and a post-hoc Bonferroni's test when needed. A Student's *t* and χ^2 tests were used for comparison of demographical and clinical data between patients and controls. Correlation analyses were done using the Pearson's test for comparison of amplitude of CHEPs and demographical, clinical and psychophysical characteristics as well as with the NCS variables. A value of $p < 0.05$ was considered for statistical significance.

3. Results

Table 1 displays data on demographic and clinical characteristics of patients and controls. The physical examination was normal in all healthy subjects and in the non-affected side of patients, and showed decreased tactile sensation in the symptomatic thigh of all MP patients. No patient had static allodynia (pressure over

Table 1
Demographic and clinical data from control subjects ($n = 14$) and MP patients ($n = 14$)

Characteristics	Controls	Patients	p^*
Age (years)	50.4 (15.2)	52.9 (12.5)	NS
Sex (male/female)	7:7	8:6	NS
Weight (kg)	73.1 (11.4)	80.8 (8.9)	NS
Height (cm)	170.2 (8.5)	167.5 (9.8)	NS
BMI	25.2 (3.0)	28.9 (3.4)	0.003
Disease duration (months)	–	20.8 (11.6)	NA
VAS-pain	–	4.3 (1.3)	NA
Sensory symptoms (%)	–	100	<0.001
Numbness	–	64.2	
Tingling	–	57.1	
Burning pain	–	71.4	

BMI, body mass index; VAS-pain, visual analogue scale for pain; NS, not significant; NA, not applicable.

* All statistical analyses were done using Student's t test, except for sex (χ^2 test).

the symptomatic zone), while 2 patients exhibited mechanical allodynia, with pain elicited by rubbing the symptomatic cutaneous region with a ball of cotton.

A summary of the mean data obtained for all tests is displayed in Table 2. Patients had unilateral SNAP abnormalities in latency, amplitude and conduction velocity of the LFCN in the affected side (Fig. 1), with absent responses in four patients, two of them with allodynia. No significant correlations were found between NCS variables and VAS-pain ($p > 0.05$ for all correlations).

The one-factor ANOVA showed significant differences in thresholds among data groups ($F[2, 39] = 25.6$, $p = 0.03$ for warm; $F[2, 39] = 21.9$, $p < 0.001$ for heat pain, and $F[2, 21] = 17.2$, $p = 0.03$ for cold sensations). Post-hoc analysis showed that differences were due to higher thresholds in the symptomatic side of MP patients than in the asymptomatic side of patients and control subjects (Bonferroni's test, $p < 0.001$ for all comparisons), with no significant differences between non-

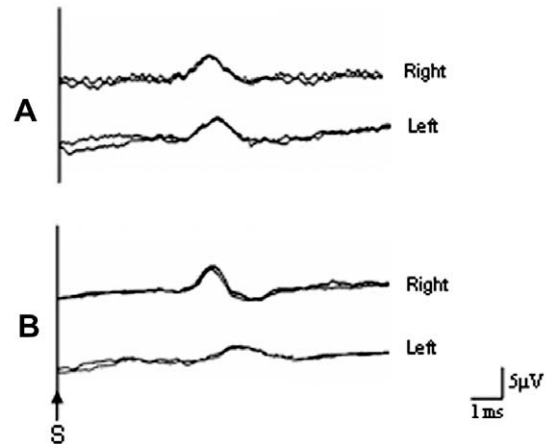


Fig. 1. Illustrative sensory nerve action potentials of the lateral femoral cutaneous nerve from a control subject (A) and a patient (B) with meralgia paresthetica in the left side. Each superimposed trace represents the average of 40 trials.

affected side and control subjects (Bonferroni's test, $p = 0.2$).

Contact-heat stimuli at 41 °C failed to evoke any brain potential in both groups of patients and control subjects. Regarding 51 °C, CHEPs were present in all subjects (Fig. 2). No differences between groups were found for latencies of N2 ($F[2, 39] = 0.08$, $p = 0.9$) or P2 ($F[2, 39] = 0.9$, $p = 0.4$). However, differences were found for N2/P2 amplitude ($F[2, 39] = 29.5$, $p = 0.001$). The amplitude of CHEPs was lower in the affected side of MP patients compared to the asymptomatic side and control subjects (Bonferroni's test, $p < 0.001$ for both comparisons).

In the 2 patients with allodynia (see black squares in Fig. 3) the mean thermal thresholds were between 39 and 40 °C for warm and between 50 and 52 °C for heat pain sensation, and their CHEPs amplitudes were between 11 and 20 μV . Fig. 3A shows the inverse correlation obtained between CHEPs amplitude and duration

Table 2
Neurophysiological data from control subjects ($n = 14$), affected and non-affected side of MP patients ($n = 14$)

Tests	Parameters	Controls	MP-NAS	MP-AS	p^*
NCS-LFCN	SNAP latency (ms)	4.8 (0.4)	4.7 (0.2)	5.4 (0.4)	0.01
	SNAP amplitude (μV)	7.7 (0.7)	7.9 (0.6)	1.8 (1.7)	<0.001
	Conduction velocity (m/s)	55.8 (5.6)	53.2 (2.6)	46.7 (3.7)	0.02
QST	Cold (°C) ^a	29.9 (0.7)	29.8 (1.0)	28.2 (1.0)	0.02
	Warm (°C)	34.7 (1.8)	35.1 (1.9)	38.5 (2.6)	0.03
	Heat pain (°C)	44.0 (2.2)	44.0 (1.9)	47.6 (2.4)	<0.001
CHEPs ^b	N2 latency (ms)	450.2 (19)	448 (13.4)	447.5 (17.0)	NS
	P2 latency (ms)	531.8 (16.2)	538 (17.2)	528.0 (17.0)	NS
	N2/P2 amplitude (μV)	49.5 (6.5)	50.1 (4.2)	29.8 (8.2)	<0.001

NCS-LFCN, nerve conduction study of the lateral femoral cutaneous nerve; QST, quantitative sensory testing; CHEPs, contact-evoked heat potentials; MP-NAS, non-affected side of meralgia paresthetica patients; MP-AS, affected side of meralgia paresthetica patients; NS, not significant.

^a Determined in 10 patients.

^b Target heat pulse temperature of 51 °C.

* One-factor ANOVA.

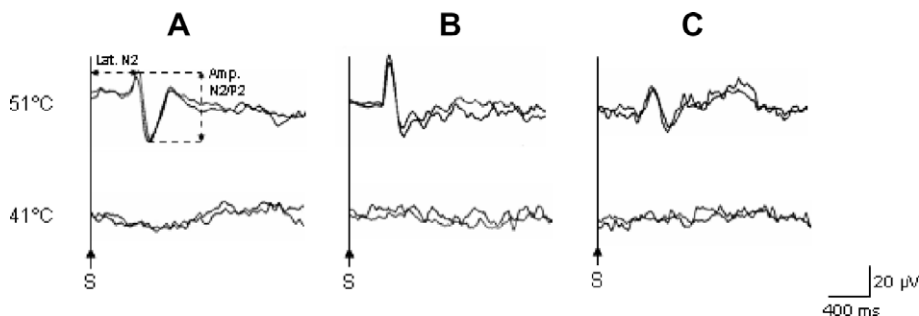


Fig. 2. Negative (N2) and positive (P2) components of illustrative contact-evoked heat potentials in a control subject (A), non-affected (B) and affected side (C) of a patient with meralgia paresthetica. Each superimposed trace represents the average of 20 trials related to target heat pulse temperatures of 51 °C (above) and 41 °C (below).

of symptoms ($r = -0.57, p = 0.002$). There was also a relatively weak inverse correlation (Fig. 3B) between CHEPs amplitude and heat pain threshold ($r = -0.18, p = 0.01$), but no significant correlations with other variables ($p > 0.05$ for all comparisons).

4. Discussion

Our study shows two main findings: (1) patients with unilateral MP had lower CHEPs amplitudes and higher

thermal thresholds in the affected side compared to the non-affected side and control subjects, suggesting a dysfunction of the small fibres within the LFCN; (2) the amplitude of CHEPs had an inverse correlation with the duration of symptoms, suggesting an involvement of small fibres late in the course of the disease.

The finding of small fibre damage in entrapment syndromes is not new. Higher thermal thresholds [7,23,51] and lower amplitude laser-evoked potentials [2] have been already described in patients with carpal tunnel syndrome. We found an inverse correlation between the amplitude of CHEPs and duration of the disease, which is in accordance with the fact that the small fibres are usually the last to be involved in entrapment syndromes [26,30]. Indeed, Borg and Lindblom [7] found abnormal thresholds of warm and cold sensations in only 15% of patients suffering from carpal tunnel syndrome. Therefore, because small fibres are affected at later stages of MP, early pain in MP must be mediated by different mechanisms.

An attractive hypothesis is the one from Melzack and Wall [28]. These authors stated that the presence of pain depended on the balance of inputs from A- and C-fibres and, consequently, selective loss of A-fibres would be expected to yield pain. However, experimental confirmation of this hypothesis has not been always possible [8,25]. Chronic and intermittent compression of the LFCN could be directly responsible for the symptoms due to the same mechanisms as the painful paresthesias experienced after release of an ischemic block [37], attributed to spontaneous activity in A-fibres [32].

However, if pain would depend mainly on large fibre activity a significant correlation between pain scores and SNAP amplitude would be expected. We did not find such correlation, which is in accordance with other authors [22,40]. This absence of correlation contrasts with the strong correlation documented between pain and NCS of patients with uremic neuropathy [1]. The difference between the two conditions is that in uremic neuropathy there is clear predominance of axonal pathology while in entrapment syndromes, nerve pathology is multifactorial and includes edema, wallerian degeneration, myelin

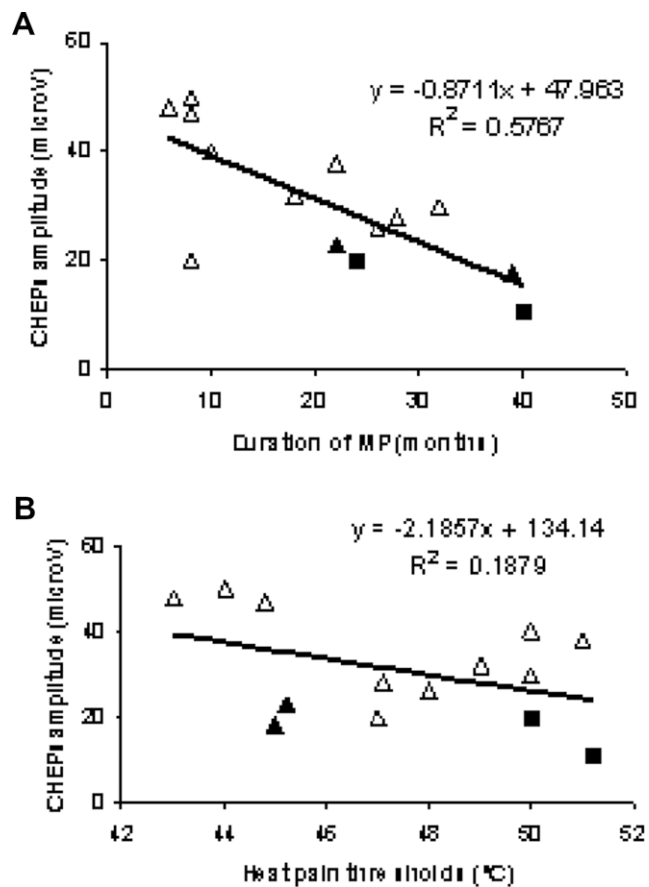


Fig. 3. Correlation graphics between CHEPs amplitude and duration of symptoms (A) and heat pain thresholds (B).

disruption and fibrosis [27,29,31]. Finally, anatomic variation in the distribution of LFCN [24] and the narrow range of the mean values for SNAP amplitudes could have contributed to the nonsignificant correlation analyses.

Our patients with MP had spontaneous pain, decreased sensation and allodynia localized in a specific neuroanatomical region. Apart from that, patients were presented with clear electrophysiological abnormalities. This picture is compatible with the diagnosis of “definitive neuropathic pain” [18,36]. Indeed, an essential part of neuropathic pain is the presence of partial or complete loss of afferent function followed by a paradoxical sensory phenomena i.e., dysesthesias [18,19]. The loss of afferent function may involve all sensory modalities, but loss of spinothalamic function, demonstrated here by the abnormalities found in thermal thresholds and CHEPs, appears to be crucial for the diagnosis of neuropathic pain [14,17,38].

However, in our patients, CHEPs amplitude did not correlate with pain scores. This was not unexpected, since the positive correlation between nociceptive-evoked potentials and subjective perception described in healthy subjects is usually disrupted in patients with chronic pain [14]. Lack of correlation between electrophysiological signs of nerve damage and subjective pain could have at least three explanations. First, pain is a positive phenomenon that may be due to hyperactivity in non-injured fibres adjacent to the lesional area [52]. Second, central sensitization could have contributed to pain in some patients, for instance in those with elevated thermal thresholds or dynamic mechanical allodynia. Unfortunately, we did not perform QST for positive sensory symptoms, as suggested by Rolke et al. [38], which would have possibly provided information on the role of central sensitization in the pathophysiology of allodynia. Third, pain may be due to non-neuropathic damage near the compression site [4]. Nerve trunk pain, for instance, is considered nociceptive, not neuropathic [6]. Peripheral nerve trunks are innervated by mechano-sensitive afferents known as *nervi nervorum*, that can be activated at the site of nerve trunk entrapment and give raise to painful neuropathic-like symptoms without identified structural lesions [12]. Therefore, the dysfunction of nerve fibres (either of large or small diameter) with subsequent central sensitization and physiological hyperactivity of *nervi nervorum* may have induce a mixed nociceptive–neuropathic type of pain in MP patients.

The correlations between CHEPs and heat pain thresholds were significant but weak. Apart from that, CHEPs were altered in some patients with normal thresholds (see black triangles in Fig. 3), indicating that the former can be more sensitive than QST in detecting thermal sensory deficits in patients with MP. Indeed, nociceptive-evoked potentials, such as CHEPs, are considered as a good alternative to QST to assess loss in heat

pain sensitivity [11,44]. However, we did not obtain any brain-evoked potential using 41 °C stimulation, even in controls, which is in agreement with some recent reports [16,46]. This is probably due to both, the unavoidable co-activation of myelinated fibres using contact-heat stimulation [34] and the insufficient synchronization of afferent inputs with 41 °C stimuli [46]. Although evoked potentials to C-fibre input have been obtained by different means (for review of the methods, see [34] their utility in the study of patients is still unclear. Therefore, QST for warm sensation was useful to demonstrate the probable involvement of C fibres in our patients.

The present study was not an attempt to introduce a new diagnostic tool for MP, but just a method of documentation of involvement of small fibres. Our study showed group differences with a substantial overlap between control subjects and patients and, therefore, it is unlikely that QST or CHEPs can be used for the diagnosis of MP in an individual basis. Also, these techniques are unsuitable for the assessment of entrapment syndromes like MP at their early stages, when small fibre function may still be spared. However, NCS of LFCN is sometimes technically difficult to perform, particularly in obese patients, and can bring false-positive results because of anatomic variations of LFCN [24]. Therefore, we think that the finding of QST and CHEPs abnormalities could support the diagnosis of MP in advanced stages of the LFCN entrapment.

In conclusion, there is clinical and neurophysiological evidence for a small fibre dysfunction in patients with MP. Because functional abnormalities in small fibres are related to the generation of neuropathic pain we believe that they contribute in part to the pain symptoms experienced by MP patients, especially in advanced stages of the disease. Additional studies of MP patients are warranted, aimed to investigate the possibility of involvement of small fibres using skin biopsy and central sensitization mechanisms of pain through neuroimaging techniques.

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